The Intrauterine Origins of Non-Insulin-Dependent Diabetes and Cardiovascular Disease

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During the past eight years research by the Medical Research Council, at Southampton, U.K., has focused on the effect of the environment in utero and during infancy in determining coronary heart disease and stroke. There are two reasons for this focus on the prenatal and early postnatal environment. First, animal experiments provide strong evidence that transient events in early life have permanent and profound effects on physiology and metabolism, though such effects may remain latent until the animal is mature [1-7]. Second, analyses of the large differences in death rates from cardiovascular disease between different areas of England and Wales have shown that they parallel similar differences in neonatal mortality in the early years of the century[8]. In those days high neonatal mortality indicated a high incidence of low birthweight, and was linked to poor maternal nutrition and physique.

The idea that coronary heart disease may have its origins in childhood is familiar, but the hypothesis that it is importantly determined by responses to the maternal environment, in utero and during infancy, is a new point of departure for cardiovascular research.

A new approach to the causes of cardiovascular disease is needed because the search for influences in the adult environment which lead to the disease has met with limited success. Cigarette smoking, obesity and lack of exercise have been implicated; evidence on excess dietary fat and the benefits of fruit and vegetable consumption has accumulated to the point where a public health policy directed at changing the national diet is prudent, even if the case is unproven. Much, however, remains unexplaned.

We do not know why rates of cardiovascular disease have declined so rapidly in many Western countries over the past twenty years. Differences in adult lifestyle go only a small way towards explaining the large differences in death rates from cardiovascular disease between one part of Britain and another. Adult lifestyle is a poor predictor of individual risk of cardiovascular disease.

Animal studies

Numerous animal experiments mostly carried out in the United States have shown that poor nutrition, and other influences which affect development during critical periods of early life, may permanently change the structure and physiology of a range of organs and tissues[1-6]. This phenomenon is known as programming[7]. A simple example is that of rats weaned onto a low protein diet for only three weeks whose insulin response to glucose is thereafter permanently impaired[5]. This impaired response is likely to reflect persisting damage to the pancreatic β cells, which develop during late foetal life and infancy. Programming occurs because organs and systems mature during periods of rapid growth in foetal life and infancy. There are critical windows of time during which maturation must be achieved; and failure of maturation is to some extent irrecoverable.

A female rat injected with a few micrograms of testosterone propionate during the first four days after birth develops normally until puberty. Only then does it become apparent that the hypothalamic neuronal substrate that mediates the cyclic release of gonadotrophins has been irreversibly altered to a male pattern when, despite adequate ovarian and pituitary function, the animal fails to ovulate or show normal patterns of female sexual behaviour[10]. The same injection of androgen given when the animal is 10 days old has no effect on reproductive function.

Nutritional deprivation in early life affects the size and DNA content of different organ systems depending on the precise time at which it occurs. In rats, a brief period of energy restriction immediately after birth causes a profound reduction in the weight of the liver, spleen and thymus, while brain and skeletal muscle are spared[2]. Energy restriction immediately after weaning reduces only the weight of the thymus.

Geographical studies

Geographical studies gave the earliest clue that cardiovascular disease might be a consequence of impaired early development of blood vessels, the liver, endocrine pancreas and other tissues. In 1985-7 we carried out a series of analyses of the distribution of cardiovascular disease in Britain. Figure 1 shows differences in death rates from cardiovascular disease between the 212 local

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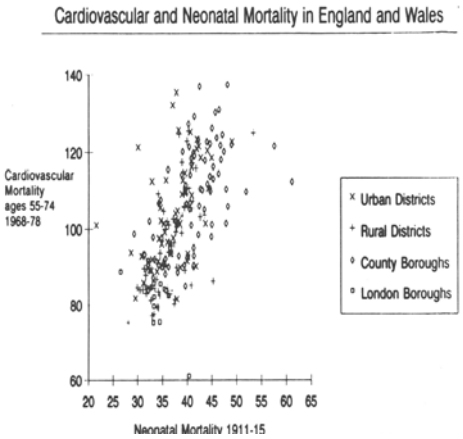

Figure 1: Standardised mortality ratios for cardiovascular disease in 1968-78 and neonatal mortality per 1000 births in 1911-15 in the 212 areas of England and Wales.

authority areas of England and Wales during 1968-78. The differences are large, greater than twofold. The highest rates are generally in northern industrial towns and in some of the less affluent rural areas in the north and west of the country. The rates correlate remarkably closely with past differences in neonatal mortality[8,9]. The horizontal axis on Figure 1 shows neonatal mortality at around the time of birth of the generation whose cardiovascular death rates are shown on the vertical axis. In the past high neonatal mortality was associated with high maternal mortality. Places with high rates from both neonatal and maternal mortality were characterised by a high prevalence of low birthweight and poor nutrition and health among mothers[11,12]. The geographical link between current cardiovascular death rates and past prevalence of low birthweight and poor maternal nutrition therefore raised the possibility that cardiovascular disease may originate through programming in utero.

The effects of programming are now being systematically explored in studies of middle-aged and elderly adults whose birth measurements and infant growth were recorded. The records were discovered by a systernatic search of archives and hospitals n Britain.

Follow-up studies

From 1911 onwards every baby born in the country of Herrfordshire was weighed at birth, visited periodically by a health visitor throughout the first year, and weighed again at one year of age[13]. Records of these visits have survived so that it is possible to trace men and women born 60 and more years ago and to relate their early measurements to the later occurrence of illness and death, and to the levels of known risk factors for cardiovascular disease. Similar long-term follow-up studies are being carried out in Preston[14] and Sheffield[15] where 50 years ago maternity hospitals made unusually detailed measurements on all newborn babies.

The first study in Hertfordshire was of 5600 men born in the eastern part of the country between 1911 and 1930[13]. The size of the sample was later increased and Figure 2 shows results for 8175 men. Those who weighed 18 pounds [8.2 kg] or less at one year of age had death rates from coronary heart disease which were almost three times greater than among those who weighed 27 pounds [12.3 kg] or more. Death rates fell progressively with increasing weight at one year. There were similar, though less strong, trends with birthweight. The same trends have recently been shown in women (Fall CHD, unpublished).

One possible explanation for the close link between early growth and cardiovascular disease is that the genes which determine low weight gain in utero and during infancy also determine cardiovascular disease. This explanation is not likely to be correct because birthweight does not seem to be strongly genetically determined. Comparisons of the birthweights of half- siblings show that whereas those related through the mother tend to have similar birthweights those related through the father do not[16]. Studies of the birthweights of first born children and mothers and daughters similarly suggest that genetic factors play only a small part in determining birthweight[17]. Neither in foetal growth nor in most cases of cardiovascular disease do purely genetic influences have a major effect and it is necessary to look for another link between them.

Insulin suggests itself as one possibility. Together with the insulin-like growth factors it is thought to have a central role in the regulation of foetal growth. Deficiency of or resistance to insulin lead to non-insulin dependent diabetes in adult life, which is associated with an increased risk of cardiovascular disease.

Non-insulin dependent diabetes

Table 1 shows the results of standard glucose tolerance tests carried out on a sample of 370 men from the Hertfordshire cohort[18]. A similar study on women has only recently been completed because change of name at marriage makes women more difficult to trace. The percentage of

men with impaired glucose tolerance, defined by a plasma glucose concentration of 7.8 to 11.0 mmol/litre at two hours, or non-insulin dependent diabetes, defined by a two hour plasma glucose concentration of 11.1 mmol/litre or more, fell progressively with increasing birthweight and increasing weight at one year. There were

Table 1

Prevalence of non-insulin dependent diabetes and impaired glucose tolerance (2 hour plasma glucose concentration ≥ 7.8 mmol/l) in men aged 59 to 70 years

Weight at one year (pounds)	Number of men	Impaired glucose tolerance or diabetes		Odds Ratio adjusted for body mass index (95% C.I.)
		No.	%	
≤ 18	23	10	43	8.2 (1.8 to 38)
-20	63	20	32	4.8 (1.2 to 19)
-22	107	32	30	4.2 (1.1 to 16)
-24	105	19	18	2.1 (0.5 to 7.9)
-26	48	9	19	2.1 (0.5 to 9.0)
≥27	24	3	13	1.0
Total	370	93	25	X^2 for trend = 14.9 ($p < 0.001$)

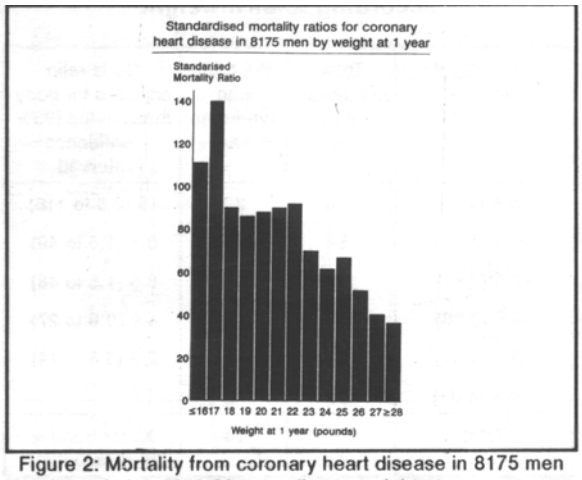

Figure 2: Mortality from coronary heart disease in 8175 men born during 1911-30 according to weight at one year.

threefold differences in the prevalence of impaired glucose tolerance and diabetes between men with the lowest and highest early weights. After adjusting for current body mass the relative risk fell progressively from 8 in men who weighed 18 pounds or less at one year to 1 in men who weighed 27 pounds or more. These trends parallel the fall in death rates from coronary heart disease with increasing birthweight and weight at one year (Figure 2).

Findings in a study in Preston confirmed these observations in men and women and extended them[19]. Glucose tolerance tests were carried out on 140 men and 126 women aged 50 years, who were born in a hospital where birth measurements were recorded in unusual detail. Table 2

Table 2

Differences in mean body size, currently and at birth, between men and women with and without non-insulin dependent diabetes mellitus or impaired glucose tolerance

	Difference (with-without)		
	Total (34 with, 232 without)	95% confidence interval	sex adjusted p-value di abetes
Current body Size			
Height (m)	-0.05	(-0.07 to -0.03)	< 0.0001
Weight (kg)	5.1	(0.9 to 9.2)	0.02
Body mass Index (kg/m^2)	3.5	(2.1 to 4.9)	< 0.0001
Waist to hip ratio (%)	4.1	(1.7 to 6.6)	0.001
Body size at birth			
Birthweight (kg)	-0.32	(-0.51 to -0.13)	0.001
Length of gestation (days)*	-2.0	(-8.1 to 4.2)	0.5
Placental weight (kg)	0.00	(-0.06 to 0.05)	0.9
Placental to birthweight ratio	0.021	(0.007 to 0.036)	0.004
Head circumference at birth (cm)	-0.9	(-1.5 to -0.2)	0.009
Length at birth (cm)	-0.6	(-1.6 to 0.4)	0.2
Ponderal index at birth (kg/cm^3)	-1.6	(-2.7 to -0.5)	0.004

shows that the 34 subjects found to have impaired glucose tolerance or non-insulin dependent diabetes had lower birthweight, a smaller head circumference, and were thinner at birth as defined by a low ponderal index (birthweight/birth length^3). They also had a higher ratio of placental weight to birthweight. The results for men and women were similar. The prevalence of diabetes and impaired glucose tolerance fell from 27 per cent in subjects who weighed 5.5 pounds or less at birth to 6 per cent in those who weighed 7.5 pounds or more. This trend was independent of duration of gestation. Low birthweight and

impaired glucose/insulin metabolism are therefore associated through reduced rates of foetal growth.

A similar study of 233 men and women in Sheffield aged 51 years (unpublished) confirmed the findings in Preston. A study of 40 men aged 21 years showed that associations between birthweight and plasma glucose and insulin concentrations can be detected in young adults[20]. This last finding and the consistent findings in the three other studies are strong evidence that the associations are not the result of confounding influences in the lifestyle of adults that are linked both to reduced foetal growth and to the later development of impaired glucose tolerance.

Insulin deficiency: In Table 3 the 370 men in Hertfordshire whose glucose tolerance was measured (Table I) are grouped according to thirds of weight at one year and thirds of current body mass (weight/height^2). The highest two hour plasma glucose concentration was found in men who failed to grow above the lowest third of infant weight but became obese as adults. Conversely the lowest two hour plasma glucose concentration occurred in men who achieved the highest third of infant weight but remained thin as adults. One explanation of this is that the men who had low weight at one year sustained impaired development of the pancreas during its period of rapid growth in foetal life and infancy[21]. This interpretation is consistent with the occurrence of impaired development of the endocrine pancreas found in babies with intrauterine growth retardation[22], and with studies in rats which show that undernutrition in early life permanently impairs the insulin secretory response to glucose[5].

Table 3
Mean Plasma Oiucose concentration (mmol/l) in men two hours after 75G oral glucose according to weight at one year and adult body mass index

Adult body mass index (Kg/m^2)	Weight at one year (pounds)			
	-21.5	-23.5	>23.5	Total
-25.4	6.6 (45)	6.1 (39)	5.8 (36)	6.2 (120)
-28	6.7 (47)	6.9 (44)	5.9 (36)	6.5 (127)
>28	7.7 (39)	7.4 (43)	6.6 (41)	7.2 (123)
Total	7.0 (131)	6.8 (126)	6.1 (113)	6.6 (370)

Insulin resisiance: Recent findings suggest that both insulin resistance and impaired β cell development are important in the pathogenesis of non-insulin dependent diabetes[23,24]. Table 4 shows the prevalence of syndrome X, a syndrome associated with marked insulin resistance, among the men in Hertfordshire.

Patients with the syndrome have impaired glucose tolerance, hypertension, high serum triglyceride concentrations and low serum high density lipoprotein (HDL) concentrations[23]. The prevalence of syndrome X fell progressively from 30 per cent in men who weighed 5.5 pounds or less at birth to 6 per cent in men who weighed 9.5 pounds or more[25]. The relative risk, after adjusting for current body mass, fell from 18 to 1.

Table 4
Prevalence of Syndrome X (Type 2 Diabetes, hypertension and hyperlipidaemia) in men according to birthweight

Birth weight Pounds (kg)	Total number of Men	Per cent with syndrome X	Odds ratio adjusted for body mass index (95% interval)
≤ 5.5 (2.50)	20	30	18 (2.6 to 118)
-6.5 (2.95	54	19	8.4 (1.5 to 49)
-7.5 (3.41)	114	17	8.5 (1.5 to 46)
-8.5 (3.86)	123	12	4.9 (0.9 to 27)
-9.5 (4.31)	64	6	2.2 (0.3 to 14)
≥9.5 (4.31)	32	6	1.0
Total	407	14	X^2 for trend = 16.0 ($p<0.001$)

Findings in Preston confirm that syndrome X is related to low birthweight in both men and women[25]. They also show that patients tended to have been thin at birth, with a low ponderal index. Insulin tolerance tests carried out on 103 subjects in Preston, either normoglycaemic or with impaired glucose tolerance, have since confirmed that low ponderal index at birth is associated with insulin resistance in adult life (Phillips DIW, unpublished). The processes which link thinness at birth with insulin resistance in adult life are not known. Studies of patients with non-insulin dependent diabetes, using a uglycaemic clamp, have shown that peripheral

tissues, particularly skeletal muscle, are an important site of insulin resistance[24]. Muscle biopsies have shown that insulin resistance is associated with a lower density of capillaries in muscle, a lesser proportion of Type 1 muscle fibres and a greater proportion of Type 2B fibres[26]. Transcapillary insulin transport is a rate-limiting step in insulin action. Babies born at term with a low ponderal index have a reduced mid-arm circumference which implies that they have a low muscle bulk as well as less sub-cutaneous fat[27]. It is therefore possible that thinness at birth is associated with abnormalities in muscle structure and function which persist into adult life and interfere with the ability of insulin to promote glucose uptake.

Hypertension

Table 5 shows that systolic blood pressure in elderly men and women fell progressively be

Table 5
Mean Systolic Pressure (mmHg) in men and women aged 64 to 71 years according to birthweight

Birth weight (pounds)	Men	Women
-5.5	171 (18)	169 (9)
-6.5	168 (53)	165 (33)
-7.5	168 (144)	160 (68)
-8.5	165 (111)	163 (48)
>8.5	163 (92)	155 (26)
Total	166 (418)	161(184)
Standard deviation	24	26

Figures in brackets are numbers of subjects

tween those who had low birthweight and those who had high birthweight[28]. No similar association was found with weight at one year, independent of birthweight, nor was infant growth found to be related to blood pressure in the Brompton study of 1895 children followed up from birth to 10 years[28]. This suggests that high blood pressure is programmed prenatally rather than during infancy.

Associations between birthweight and adult blood pressure have been found in a national sample of men and women born in Britain in 1945[29,30], in men and women in Preston [14] and in Sheffield (Martyn CN, unpublished). These associations do not depend on shortened gestation[13,30,31]. It can be concluded that high blood pressure is initiated by processes associated with reduced growth in utero. Similarly to impaired glucose tolerance the relation between blood pressure and reduced foetal growth is not confined to babies with intrauterine growth retardation defined by birthweight at the lowest centiles. It is also seen in babies of around average weight.

Though the relation between systolic pressure and birthweight becomes evident in the early months of life it grows progressively stronger with increasing age[28]. An interpretation of this is that the association between reduced foetal growth and blood pressure is initiated in utero, but amplified in later life.

The existence of initiating and amplification mechanisms in the aetiology of essential hypertension was first postulated by Folkow[32]. We can speculate on the processes which underlie them. The initiating process could be changes in foetal blood flow, perhaps resulting from perfusion of a large placenta, since large placental size in relation to foetal size is a strong predictor of blood pressure in adults[14]. Alternatively it might be increased activity of a trophin or mitogen leading to changes in the vessel wall and subsequently a rise in blood pressure. Suggested trophins include growth hormone, insulin and insulin- like growth factor I (somatomedin C) sympathetic nerves, catechol-amines, and angiotensin II[33]. A wide variety of endocrine changes have been demonstrated in growth retarded fetal sheep: these include lower blood concentrations of insulin and increased concentrations of adrenaline and noradrenaline[34].

The feedback mechanism which amplifies the initiating effects with age could depend on progressive changes in the structure or compliance of blood vessels. In humans and in animals vascular structure and compliance change with haemodynamic load[35]. An increase in peripheral resistance and pulse pressure in early life could alter structure and reduce compliance, which in turn would increase pulse pressure. A feedback mechanism could thereby become established[36].

Lipid metabolism and haemostatic factors

Studies of serum lipid concentrations among adults in Hertfordshire and elsewhere show that serum total and low-density lipoprotein (LDL) concentrations are associated with specific patterns of foetal growth and the type and duration of infant feeding. Detailed description of these findings is beyond the compass of this review. Early results have been published[37,38]. They

echo experiments on animals. The early nutrition of rats has been shown to determine the response to a dietary fat challenge in adult life[3]. In baboons serum concentration and biliary excretion of cholesterol are strongly influenced by the type of diet that they were fed in the neonatal period[6].

Studies of plasma fibrinogen concentrations in adults, the strongest single predictor of cardiovascular disease, have shown that high concentrations, associated with increased risk, are found in men who were short at birth in relation to their head circumference, and had low weight gain in infancy[39]. Though short, these babies had around average birthweight, a further illustration that sub-optimal foetal growth, as indicated by adverse long term outcomes, extends through the whole range of prenatal and infant weight gain. The associations between plasma fibrinogen concentrations and shortness at birth are thought to reflect impaired development of the liver during a critical period in late gestation.

Confounding variables: Critics of research into programming maintain that people who had reduced growth in utero and during infancy may continue to be exposed to an adverse environment in childhood and adult life, and it may be this later environment which produces the effects now being attributed to impaired early development[40]. This criticism is unlikely to be correct. Relations between reduced early growth and adult disorders are strong and graded. The size of the relative risks, such as those shown in Table 4, has to be compared with the much smaller risks associated with adult lifestyle. For example, the relative risk of coronary heart disease associated with heavy cigarette smoking is around 2.0. It is unlikely that an unknown confounding variable related to adult lifestyle would produce the large and graded relations shown in Tables 1 and 4. Such a confounding variable would have a stronger effect on the risk of non-insulin dependent diabetes or syndrome X than any variable hitherto identified and its existence is likely to have been known already or at least suspected.

Maternal nutrition

The conclusion that coronary heart disease, stroke, non-insulin dependent diabetes, hypertension, and abnormalities of serum lipids and haemostatic factors are programmed in foetal life poses a number of questions. What are the influences which alter foetal growth? How does the foetus respond? How are the long-term cardiovascular, metabolic and endocrine consequences programmed? Knowledge is still scanty, but it is possible to set out a broad framework within which these questions can be explored[41].

Table 6
Mean systolic blood pressure (mmHg) of men and women aged 46 to 54, born after 38 completed weeks of gestation, according to placental weight and birth weight.

Birth weight (pounds)	Placental weight (pounds)				
	≤ 1.0	- 1.25	- 1.5	> 1.5	All
- 6.5	149 (24)	152 (46)	151 (18)	167 (6)	152 (94)
- 7.5	139 (16)	148 (63)	146 (35)	159 (23)	148 (137)
> 7.5	131 (3)	143 (23)	148 (30)	153 (40)	149 (96)
All	144 (43)	148 (132)	148 (83)	156 (69)	149* (327)

*** Standard deviation = 20.4**
Figures in brackets are numbers of subjects.

The intrauterine environment is the major influence on foetal growth. It determines nutrient and oxygen supply to the foetus. In addition the mother actively constrains foetal growth. This is demonstrated by the strong relation between birthweight and mothers' height. Normal maternal constraint of foetal growth has also been shown in embryo transfer and cross-breeding experiments: a foetus transferred to a larger uterus will achieve a larger birth size[42]. A baby's birth measurements, however, predict adult disorders independently of maternal pelvic size[15]. Discussion must therefore focus on influences which determine foetal nutrition, rather than on the physiological constraint of foetal growth by the mother.

Table 6 shows the mean systolic pressure of men and women in Preston, aged 50, who were born at term (38 weeks of completed gestation)[43]. The men and women are divided into three birthweight groups, and four groups of placental weight. There was, as expected, a fall in blood pressure associated with increasing birth weight. There was also an unsuspected increase in blood pressure with increasng placental weight. Subjects with mean systolic pressures of 150 mmHg or more comprise a group who as babies were relatively small in relation to the size of their placentas.

In man and animals disproportionately large placental size may be a consequence of maternal undernutrition. It occurs in babies whose mothers were anaemic during pregnancy[44,45]. It can be produced in sheep by depriving the ewe of food in early pregnancy[46,47]. We therefore suspect that maternal undernutrition may be an important influence in determining high blood pressure in the next generation. Recent studies of 4 year old children in Salisbury have shown similar associations between birth weight, placental weight and blood pressure as were found in older people[31]. We can therefore conclude that maternal undernutrition still affects foetal growth today, a conclusion that is consistent with the high incidence of pregnancy anaemia[31,45].

Examination of birth measurements additional to weight identifies two groups of men and women who develop high blood pressure[41,43]. One group had below average weight and head circumference at birth and a low ponderal index. Such 'thin' babies have been labelled as having foetal malnutrition[48]. They have been shown to have high foetal heart rates at 18 weeks of gestation[27]. Their impaired growth may therefore result from influences which take effect in midgestation. A second group of babies who develop high blood pressure have above average birth weight and head circumference but below average length. These 'short' babies have 'asymmetrical' growth retardation, thought to result from slowing of growth near term[49]. The mechanisms by which these two groups of babies subsequently develop high blood pressure may differ because of the different times when they were subject to adverse influences. Thin and short babies have different physiology and metabolism in adult life. Thin babies tend to develop insulin resistance and syndrome X[25]: short babies develop raised plasma concentrations of fibrinogen[38]. Both thin and short babies develop cardiovascular disease[15].

Intrauterine growth retardation

The relations between early growth and cardiovascular disease and its risk factors are continuous. Death rates from cardiovascular disease and the prevalence of its risk factors fall progressively up to the highest values of birthweight and weight at one year. If the criteria for successful foetal growth include adult health and longevity these findings reinforce the view that babies with significant intrauterine growth retardation need not necessarily be 'light-for-gestational age'[50]. Intrauterine growth retardation seems to be widespread. It affects many babies whose birthweights are within the normal range, not just a few babies who are recognised clinically by their unusually small size and high risk of perinatal complications and death. We .need to know more about the effects of intrauterine growth retardation on different organs and systems in the human foetus.

Conclusion

Research into the nutritional and other influences that modulate the growth of the foetus and permanently programme its metabolism is now a priority. It may hold the key to prevent cardiovascular disease and other important disorders in adult life.

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